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REMARKS

Support for the Amendments to the Claims can be found at: Claim 4 "all"- p.3/line23; 4/18;6/18; 6/25;10/16; 11/31; 13/19; 18/19; 18/27; 21/29; 27/28, etc.; Claim 9 - Table G beside "Classification Level", also Fig. 12; Claim 47 - previous Claim 4.

For convenience, pages 2 and following of the Official Action are set forth below, with Applicants' remarks interspersed.

> ***DETAILED ACTION***
> *A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/8/2009 has been entered.*
> *Applicants have amended their claims, filed 9/8/2009, and therefore rejections newly made in the instant office action have been necessitated by amendment.*
> *Applicant has newly added claim 47 in the response filed 9/8/2009, which has been acknowledged and entered.*
> *Claims 4-10,19,21,23,24,28-29, and 39-47 are the current claims hereby under examination.*
> ***Claim Rejections - 35 USC § 101 Response to Arguments***
> *Applicant's arguments, filed 817112009 and 9/8/2009, with respect to the rejection of claims under 35 USC 101 have been fully considered and are persuasive because of applicant's amendments and arguments. Therefore the rejection has been withdrawn.*

The Examiner is thanked for withdrawing the 35 USC 101 rejections.

> *Claim Rejections - 35 USC § 112 First Paragraph Response to Arguments*
> *The following rejection is being newly applied, which has been necessitated by amendment:*
> *Claim Rejections - 35 USC § 103*
> *Response to Arguments*
> *[Page 3} Applicant's arguments, filed 8/7112009 and 9/812009, with respect to the rejection of claims under 35 use 112 Second have been fully considered and are persuasive because of applicant's amendments and arguments. Therefore the rejection has been withdrawn.*

The Examiner is thanked for withdrawing the 35 USC 112 rejections.

> *The following rejection is being newly made upon further considerations:*
> *The following is a quotation of the second paragraph of 35 U.S.C. 112: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated*

where the signature probes are comprised of a nucleic acid analog comprising

PNA, 2'-O-methyl DNA or analog thereof. The utility of complementarity is taught on page 3 line 12 and page 5 line 2 of the specification.

> *[Page 4] Claim 9 and all claims dependent thereon are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for performing the method wherein the defined grouping comprises a moiety selected from the group consisting of: a specific genus, species, serotype, and another grouping below the species level, but does not reasonably provide enablement for the moiety of race. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to define a grouping on the tree of relationship based on race, and practice the invention commensurate in scope with these claims. In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.*
> *In considering the factors for the instant claims:*
> *a) In order to practice the claimed invention one of skill in the art must make or perform the method of claim 4, specifically step D wherein one of the nodes includes race, i.e. a defined grouping on the tree of relationship comprises a moiety of race. For the reasons discussed below, undue experimentation would have been required to practice the claimed invention.*
> *b) The specification provides guidance for making and using a defined grouping comprising a specific genus, species, or serotype, but does not provide guidance for defining a grouping based on race. In other words, the specification does not provide guidance as how to go about assigning probes or establishing genetic relationships within the tree based on "race."*
>
> *[Page 5] c) The specification does not provide any working examples of how to establish or define genetic relationships within the tree based on race, such as what probes to assign.*
> *e) State of the art is complicated and unpredictable.*
> *f) The skill of those in the art of molecular biology is high.*
> *g) The prior art is devoid of how to divide groups genetically within a phylogenetic tree based on race, thus one of ordinary skill in the art would not know how to establish such genetic relationships within the tree based on race. One of skill in the art would not know how to assign or create a database of signature probes or establish genetic relationships within the tree based on race.*
> *The skilled practitioner would first turn to the instant specification for guidance to practice methods of how to establish genetic relationships within the tree based on race. However, the instant specification does not provide specific guidance to practice these embodiments. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art is devoid of such teachings. Finally, said practitioner would turn to trial and error experimentation to determine how to create such a tree of relationship based on race. Such represents undue experimentation.*

Claim 9 now reads: "9. [Currently Amended] A method of claim 4 wherein the most narrowly defined grouping on the tree of relationship comprises a moiety selected from the group consisting of: a specific genus,

~~a~~ specific species, ~~a race,~~ subgroups; strain, tribe and serotype ~~or other well defined grouping below the species level~~.

Claim Rejections- 35 USC 112 Second Paragraph
Applicants' arguments. With respect to the rejection of claims under 35 USC 112 Second have been fully considered and are persuasive because of applicant's amendments and arguments. Therefore the rejection has been withdrawn.

The Examiner is thanked for withdrawing the 35 USC 112 Second Paragraph rejections.

The following rejection is being made upon further considerations:
The following is a quotation of the second paragraph of 35 USC 112:
[[Page 6] The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
Claims 28-29 and all claims dependent therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
Claim 28 and all claims dependent therefrom comprises a step, which is unclear as to what information it provides from the "formula." In other words, the step comprises calculating a "signature quality function" using a formula, which comprises the presence of sequences in a particular group of organisms or viruses and their presences in other organisms NOT belonging to that group of organisms or viruses, i.e. the sequences appear to belong to any and all groups. Therefore, it is unclear as to what comprises the "single formula" and what information is derived from it when a sequence that belongs in anything and everything is included. Clarification via clearer claim wording is required.
Claim 29 and all claims dependent therefrom comprises two formulas for which values of "Os" are calculated, wherein it is vague and indefinite as to which formula is used for the calculation. The step of claim 29 recites calculating the value of Os by "the equation" and then recites two equations (one not apparently being the simplified version of the other) for which Os can be calculated. Thus it is vague and indefinite as which equation is being used for said calculation. Clarification via clearer claim wording is required;

The amendments now correct a typographic mistake by cancelling "N_{GI}" and correcting to read – N_{GT} --. This makes the same three elements appear in each of the two equations and makes the two equations algebraically equivalent, as was obviously intended. The second equation is now properly the simplified version of the first equation.

A similar correction is made in Claim 23. Applicants regret the errors and thank the Examiner for noting them.

[Page 7] The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
Claims 4-9, 19,21,24, and 39-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ebersole et al. (US PIN 6,797,817).
The claims are directed to a method for determining the genetic affinity of organisms or viruses in a test sample containing a nucleic acid comprising the steps of:
A) Obtaining or creating a nucleic acid sequence database of the same target nucleic acid, from all organisms or viruses that will be incorporated into the determination;
[Page 8] B) Obtaining or developing a bifurcating node phylogenetic tree having multiple nodes that establishes the genetic affinity between the organisms or viruses included in the nucleic acid sequence databases;
C) Optionally computationally fragmenting each target nucleic acid sequence such fragmentation being performed in a programmed computer so as to create a subsequence database of nucleic acid subsequences of length N that occur in at least two sequences in the nucleic acid database, where N is at least seven;
D) Tabulating in a programmed computer the extent to which the presence of each particular nucleic acid sequence of length N is characteristic of each node in the bifurcating node phylogenetic tree of genetic relationship by examining the occurrence frequency of each subsequence in the target nucleic acid of the organisms and viruses encompassed by or not encompassed by each node in the tree, to create a database of characteristic signature sequences;
E) Deriving a plurality of signature probes from a signature-database of characteristic signature sequences that will be complementary to a portion of the target nucleic acid sequence of the organism or virus if the signature sequence is present;
F) Hybridizing the signature probes to the target nucleic acid obtained from the test sample under conditions where a detectable signal will be produced by signature probes that hybridize to the target nucleic acid of the organism or virus and detecting such signals;
G) Identifying the nodes in the bifurcating node phylogenetic tree of genetic relationship that are represented by the signature probes that produced detectable [Page 9] signal, in order to determine the genetic affinity of the organism or virus in the test sample.
With regards to limitations of claims 4, 40, 43, and 45: Ebersole et al. teach at Col. 9, lines 35-45 that a phylogenetic Tree of Life was obtained and used for extracting sequences that represented the major microorganism domains, Bacteria and Archeae, which could be used as signature sequences for obtaining signature probes for testing for the presence of dechlorinating bacteria. Ebersole et al. further teach at the abstract, Figs. 1 - 2, and col. 5. lines 27-34, that the 16s rRNA regions, Le. the target nucleic acid, are analyzed from the samples and organisms wherein their profiles/sequence database have been created. which reads on steps A) - B).

The applicant's invention is focused on determining the genetic affinity of organisms or viruses in a test sample (abstract-lines 14-15; p7 lines 11-12; and other places). This is distinctly different from determining genetic identity, which is the object in Ebersole. Ebersole seeks to determine if a specific type of dechlorinating bacteria, e.g. bacteria having the genetic identity *Dehalococcoides*, is present in the test sample. Ebersole must pre-select a subset of organisms to look for, and is completely uninformative if none of those organisms is present. In contrast, the Applicants' invention does not need to specifically identify what is in the test sample. Instead, the instant invention seeks to determine the grouping in the context of a preexisting (or calculated as needed) phylogenetic structure (e.g. tree of relationship) that the unknown organism in a test sample belongs to. In other words, the question is: which grouping does the test sample bacterium or viruses have the greatest genetic affinity to? The result in some cases may be very specific, perhaps revealing a genetic affinity to a specific species, whereas in other cases the organism might be found to be a member of a large grouping such as the Firmicutes with no affinity for any of the specific genera included in the reference tree that comprise the Firmicutes.

Of special note, even if the organism in the test sample is entirely new to science, it will typically be possible to gain some insight to its genetic affinity as long as it is encompassed by the reference tree. If that reference tree includes Bacteria and Archaea, then some insight will always be obtained unless the organism represents an entirely novel grouping that is neither Archaea nor Bacteria (most unlikely). This is a valuable advantage of the present invention which is unobvious even after a reading of Ebersole. Thus, the "subject matter as a whole" would not be obvious under 35 USC 103(a).

Because Ebersole is seeking to determine genetic identity rather than genetic affinity, a variety of approaches are taught in Ebersole that are specific for his purpose but actually *teach away* from the instant invention. Indeed, at the time of the applicant's invention it was widely believed that a microbial detection method could not be designed without prior knowledge of what is to be detected. Thus, Ebersole focuses attention on how to detect a specific anticipated bacterial grouping. The failure to recognize the value of seeking to instead determine genetic affinity, is precisely what leads Ebersole and many others (even to this day) to adopt probes that seek specific identity of one group at a time. This illustrates the non-obviousness of the Applicants' invention.

Ebersole is not "G. Identifying the nodes in the bifurcating phylogenetic tree of genetic relationship that are represented by the signature probes that produced detectable signal, in order to determine the genetic affinity of the organism or virus in the test sample." as recited in Claim 4. Because Ebersole is seeking to identify a specific grouping, the purpose for which a tree is utilized is quite distinct from the present invention (col 9, lines 35-45). Ebersole does not use the tree to define genetic affinity as recited in present Claim 4 and as taught in the Specification at page 9, lines 11-13.

Instead, Ebersole 's tree is used only during his assay design phase to select diverse sequences that are then aligned. This alignment step is done in order to identify a "probable region" (Ebersole col 9, line 40-42) within which Ebersole then looks for signature sequences. The Applicants' invention does not use and would not benefit from sequence alignment. Ebersole's sequences are "selected" (Ebersole Col 9, line 36), which implies that all are not used. It is further made clear, (Ebersole col 9, line 43-45) that the signature sequences ultimately found should be unique to the target grouping. This procedure of Ebersole *teaches away* from the

present invention by suggesting that alignment is useful or even essential and that signature sequences are only found in specific signature regions.

In Applicants' claimed invention, the tree is used to define the *genetic affinity* between various groupings that are being considered. Applicants use sequences from *all* the groupings under consideration, (e.g. not an exclusive set of selected sequences). Applicants' tree is thus not used in any way to "select" sequences, or sequence regions to be considered. Indeed alignment is not used, nor would it be useful in Applicants' method. Instead, every portion of *all* the sequences used is considered. Moreover, the characteristic sequences found do not need to be unique to a particular target grouping – even sequences associated with disparate groupings can contribute to an informative result in Applicants' claimed method. For example, given the example tree (page 56) one finds that there are in fact 13 subsequences of length 15 that with a Qs score of at least 0.8 are highly characteristic (e.g. can serve as signatures for) node 5547 (page 5, Table F). However, none of these subsequences is uniquely characteristic of node 5547. If one lowers the Qs score requirement to the 0.6-0.8 range the number of potentially useful subsequences of length 15 rises to 52. Ebersole fails to recognize this fact that sequences associated with disparate groupings can contribute to an informative result.

> *Step C) is an optional step, not necessarily performed in the instant method. However, Ebersole et al. at col. 5. lines 40-45 and col. 9, lines 11-19 and line 46 teach identifying consensus sequences, which are subsequences which occur most frequently in the 16S target nucleic acid of the organisms from which a 16s DNA profile was created. Ebersole et al. further teach at col. 9. lines 54-56 examples of the consensus sequences wherein the sequences are of length 7 or more (see SEQ ID NO: 34), which reads on limitations of step C).*

Ebersole defines consensus sequences (Ebersole col 5, lines 40-45) as "as the sequence of the set of bases where a designated base is the one that occurs most often at each position in the 16S sequence". It is a misinterpretation of Ebersole to

say "...consensus sequences, which are subsequences that occur most frequently in the 16S rRNA target nucleic acid." Consider the following example of five sequences and the resulting consensus sequence:

Seq 1: AUCAGGGACCCAGUC

Seq 2: AUGAGGGUCCCAGAC

Seq 3: ACGAGGGUCGCAGUC

Seq 4: CUGAGGAUCCCAGAC

Seq 5: AUCAGGGACCCAGUC

Consensus: AUGAGGGUCCCAGUC

The consensus sequence is constructed in accordance with Ebersole's procedure (Ebersole col 5, lines 40-45). In particular, following alignment at each position the base that is most common in the data set (sequences 1-5 in the example) is chosen. The resulting consensus sequence is in fact *not* the most common sequence in this data set. The most common sequence is sequence 1, which occurs twice (as does sequence 5). In fact, not only is the consensus sequence not the most common sequence, it actually *never occurs* in the example data set of five sequences.

Thus, in accordance with optional step C of claim 4, a subsequence obtained as a result of construction from a consensus sequence would not even be considered in the Applicants' invention unless it occurred at least two times in the data set. Indeed, even without optional step C, such a consensus sequence would teach away from the Applicants invention that teaches that "those sequences that never occur are not signature sequences" (Specification Page 6, line 18). In fact, Ebersole's use of consensus sequences teaches away from the Applicants' invention by suggesting that it might be useful or even necessary to process the sequences being considered together in some manner. Applicants' invention individually examines every possible subsequence of length N at every node in the

tree (page 6 lines 15-16). Optional step C of Claim 4 [also now recited in dependent Claim 43] computationally simplifies this process by pointing out that subsequences that occur once or not at all need not be examined. This is in sharp contrast to Ebersole, as illustrated by the above example.

> *Ebersole et al. further teach at col. 4, lines 55-67 and col. 5, lines 1-4, lines 40-45, col. 8,lines 1-19, col. 9, lines 11-19 and lines 54-56 using sequence analysis software in a computer to analyze the consensus sequence, wherein the consensus sequences were found in each decholorinating organism, and that the use of particular sequences, Le. signature regions/sequences, may be used to identify decholorinators as well as for genetic sub-typing of species.*

Ebersole teaches the use of publically available sequence analysis software of various types, e.g. GCG, DNASTAR (contains Megaalign), BLASTP, BLASTN, BLASTX, (Col 8 lines 8-12,; col 9 40-41). These tools are primarily used by Ebersole to align sequences, e.g. Ebersole Figure 1 and 2 to facilitate visual comparison or to construct consensus sequences. Ebersole's construction and use of consensus sequences teaches away from the Applicants' invention that utilizes the distribution and frequency of occurrence of individual subsequences that occur at least twice in the dataset used. In fact, as discussed above consensus sequences may themselves never occur in the data set. The computations essential to step D of claim 4 and claim 45 involve the computation of occurrence frequency by which each subsequence of length N of at least length 7 is encompassed by or not encompassed by every node in the tree. This computation is not done by using the sequence analysis software cited by Ebersole. These computations preferably involve calculation of a signature quality function for each subsequence of length 7 or more at each node in the tree as described in Applicants' revised claim 10.

> *Furthermore, Ebersole et al. teach at col. [Page 10] 9, lines 46-54 that signature regions of subsequence length N (7 or mare) were analyzed and found to be characteristic of different organisms, which reads on limitations of step D) and claim 45.*

Ebersole's Line 64 begins "within the 16S rDNA profile defined by

comparison of the isolated dechlorinators ...." Signature profiles as defined by Ebersole (col 5 lines 29-30) are complete 16S rRNA sequences from particular organisms. Thus, Ebersole is developing signature sequences and signature regions from complete sequences, not subsequences as is done in claim 4 optional step C, and claim 4 step D, and claim 45 of the Applicants' invention.

> *Ebersole et al. teach at col. 4, lines 55-67 and col. 5, lines 1-4, that sequence profiles, from which signature probes are derived, may be used to identify and subtype bacteria with similar metabolic pathways. Therefore, a signature probe may be used to identify a dechlorinated bacteria and/or bacteria with similar metabolic pathways, such as subspecies of decholorinates, which further reads on steps E) - G).*

The examiner points out that Ebersole et al. teach at col. 4, lines 55-67 and col. 5, lines 1-4, that sequence profiles, from which signature probes are derived, may be used to identify and subtype bacteria with similar metabolic pathways. As stated above, signature profiles as defined by Ebersole (col 5 lines 29-30) are complete 16S rRNA sequences from particular organisms. Ebersole, is deriving his signature sequences from visual comparisons of alignments of these complete sequences. The Applicants' method instead relies on identifying characteristic subsequences of length N where N is at least 7 from the entire set of subsequences of length N. Complete sequences are fragmented as in Claim 4 optional step C, claim 4 (specification page 6 lines 16-20) step D, and claim 45. The applicants invention focuses on examining the signature potential of individual subsequences (abstract lines 1-2, lines 20-25 ; etc). As per claim 4 part D "the occurrence frequency of each subsequence in the target nucleic acid of the organisms and viruses encompassed by or not encompassed by each node" is determined. Thus, the instant invention breaks the complete sequences into subsequences and then examines all (restricted when optional step C is employed) the subsequences of length N to identify subsequences that are characteristic of various nodes in the

tree. This procedure is not done by Ebersole who instead aligns *complete* sequences and then, in the design phase visualizes differences to design probes which are then subsequences. Subsequences are never created to assist in the design process as is done in the Applicants' invention. The failure of Ebersole to examine the signature potential of individual subsequences as is done in step D of claim 4 distinguishes the Applicants' invention.

Ebersole further teaches at col. 4, lines 55-67 and col. 5, lines 1-4 that the "sequence profiles", from which his signature probes are derived, may be used to identify and subtype bacteria with similar metabolic pathways. As noted previously, Ebersole's claim that his sequences can be used to identify organisms with similar metabolic properties is suspect. In fact, strains of *Dehalobacter, Desulfuromonas, Dehalospirillum, Desulfitobacter*, and even *Enterobacter* sp strain MS1 have "similar metabolic properties", e.g. the ability to dechlorinate (http://www.microbe.com/census_remediation_targets.html) tetrachloroethene (PCE) and TCE (trichloroethene).

> *Ebersole et al. at col. 5, lines 34-39, col. 6, lines 31-34, col. 6, lines 58-67, and col. 7, lines 1-9 teach using signature sequences for generating probes and defines the use of probes and hybridization as such that is consistent in the art, which produce detectable signals, which further reads on step E). Ebersole et al. further teach at col. 2, lines 51-65, the use of signature probes in hybridizing to identify sequences such that a signal is detectable, which further reads on step F)*

With reference to all of the examiners comments up to this point Applicants request that the following should be considered: In claim 4 step D and claim 45 the present Applicants' invention recognizes that every subsequence of length N is potentially useful as a characteristic signature of each node in the bifuricating tree and hence all must be considered at each node. At page 9 lines 46-54, Ebersole examines signature regions wherein the sequences of organisms belonging to the target group show variation from other sequences. Ebersole's sequence regions are claimed to be unique to the dechlorinating bacteria and hence useful in specific identification of organisms belonging to this group. In providing this process,

Ebersole is teaching *away* from the present invention by implying that a sequence must be characteristic of one specific node to be useful. Ebersole never teaches that a sequence that is characteristic of multiple nodes would also be useful. Indeed, Ebersole never attempts to examine the extent a subsequence of length N is characteristic of any node other than the one of interest. Although, the subspecies within the group of dechlorinating bacteria might be assigned a nodal structure, Ebersole does not and need not determine this structure, so Ebersole is teaching that consideration of the group as a single node is sufficient.

In contrast, the present invention seeks and uses subsequences of length N that are characteristic of multiple nodes in the tree (page 7 lines 1-4). If a particular sequence of length N were present in all the bacteria known to belong to both the dechlorinating group and also the genus *Nostoc* (a cyanobacterium), Ebersole would discard it as not being unique. In fact, in the applicant's invention such a subsequence would be retained as recited in Claim 4 step C. When a probe targeting this subsequence were used in combination with probes expected to target other groupings, e.g. cyanobacteria in general, it would become clear whether the unknown were a dechlorinating bacterium or *Nostoc*. In the present Applicants' invention, probes targeting multiple signature sequences are always used and multiple nodes are always targeted. In fact the larger the portion of the nodes in the tree that can be targeted the better the result. In the Specification at page 56, Table E, subsequences of length 15 allowed 86.37% of the nodes in a representative bacterial tree based on 16S rRNA to be targeted. In contrast, when Ebersole uses multiple probes they all target members of the *same single target* grouping (e.g. the dechlorinating bacteria).

Ebersole at column 9 lines 46-54, states "Within the 16S rDNA profile defined by comparison of the isolated dechlorinators (see Figs 1 and 2) four signature regions showed considerable variation from the known sequences..." The examiner states that this passage means "that signature regions of subsequence length N (7 or more) were analyzed and found to be characteristic of different organisms". An examination of Figure 1 reveals that it is a sequence alignment of known 16S rRNA sequences from various dechlorinating bacteria. Each sequence included is a complete 16S rRNA sequence, not a subsequence. The use of alignment teaches away from the Applicants' method which does not use alignment and in fact uses the target sequences in unaligned form as is done in the example provided in the specification (page 15, line 6). These unaligned sequences are subsequently fragmented, (claim 4 optional step, Claim 4 step D, and Claim 45) so that the signature properties of individual subsequences can be examined) page 6 lines 14-27 and page 7 lines 1-7) In Ebersole's Figure 2, an *E. coli* sequence is added to his alignment and as a result it is possible to visualize places (e.g. Ebersole's signature regions) where the dechlorinating bacteria sequences strongly differ from the *E. coli* (and presumably other 16S rRNA sequences though only *E. coli* was apparently used). Ebersole's "different" organisms are in fact all known dechlorinating baxcterial strains belonging to Ebersole's target group. Ebersole's identification of signature sequences is apparently visual with no effort made to find all such sequences because Ebersole only examines his signature regions. In the end Ebersole identifies a signature sequence that is longer than length 7. However, this length is simply fortuitous. Ebersole wants it to be as long as possible to facilitate hybridization but makes no considerations with regard to length when actually looking for potential signature sequences.

Ebersole's procedure is not the procedure recited in Applicants Claim 4 step D or claim 45. In step D, Applicants recite examining the utility of all subsequences of length N, not just those in nebulous signature regions. Moreover, Applicants do this examination for every node in the tree, not just a single node such as Ebersole's node containing dechlorinating bacteria. Variants among the dechlorinating bacteria are not assembled (no tree construction step made or alluded to at this point in the procedure) into nodes by Ebersole and hence knowledge of the interrelationship between such variants is not used by Ebersole when identifying his signature sequences. In effect, Ebersole is treating the dechorinating bacteria as a single node. In the instant invention the, Applicants teach tabulation of the the occurrence frequency of each subsequence of length N within *and without* of each target group. Ebersole's procedure described at Ebersole column 9 lines 46-54 and Figures 1 and 2 provides no examination of occurrence frequency, whatsoever, nor does it assure that all possible characteristic signature sequences are found. In fact, even unique signature sequences may avoid detection using Ebersole's approach (col 9, lines 40-45) as they may occur outside of the signature regions from which signature sequences are sought. Ebensole's Table 2 at Column 21 tabulates specific 16S rRNA sequence changes seen in various dechlorinating bacteria but does not tabulate occurrence frequencies in subsequences of at least length 7.

> *Ebersole et al teach at col. 8, lines 38-40 that the sequences are useful for the identification of new dechlorinating bacteria, as well as for sub-typing strains of Dehalococcoides ethenogenes. Furthermore, Ebersole et al. teach at col. 9, lines 19-40 that sequences used for obtaining probes and closest or nearest organisms to these sequences were determined, which further reads on step G).*

The argument is being made that Ebersole's node of dechlorinating bacteria actually contains within it multiple additional nodes, e.g. the sub-types. If one accepts this view, then what is the phylogenetic relationship between these various

subtypes? If Ebersole is relying on a phylogenetic tree as in the instant invention, then why is such a tree not calculated or obtained from elsewhere? The Applicants' invention requires (newly revised claim 4 part B and claim 40) that the phylogenetic tree used establish relationships between all the nodes being considered. In fact, the failure to utilize a tree in the manner of the Applicants' invention illustrates that the Applicants' invention is in fact distinct from Ebersole. This point is further emphasized by the fact then when examining subtypes, Ebersole does not and can not examine the occurrence frequency of each subsequence in the target nucleic acid of length N that is encompassed by or not encompassed by each node in the dechlorinating cluster. The reason this is true is that in the absence of a tree of phylogenetic relationships, he does not know all the nodes that are actually present. Ebersole (col 23 lines 5-41) instead tabulates differences seen in the variants in detail in order to design unique probes that encompass the variation seen. However, a tree of relationships is never needed and hence never actually constructed. This reaffirms that Ebersole is focused on determining genetic identity rather than genetic affinity.

> *Ebersole et al. suggest, but do not explicitly teach tabulating the extent to which the presence of each particular subsequence of length N is characteristic of each node in the bifurcating phylogenetic tree of genetic relationship by examining the occurrence [Page 11] frequency of each subsequence in the target nucleic acid to create a database of characteristic signature sequences.*
> *Ebersole et al. suggest this because they teach at col. 5, lines 40-45 and col. 9, lines 11-19 and lines 46-56 using software to analyze the consensus sequence, which are a set of bases which occur most often in the 16S sequences of the organisms and are characteristic of the group of decholorinating organisms.*

At his col 9 lines 11-19 Ebersole describes a procedure for sequencing a portion of the 16S rRNA of additional organisms that might belong to the dechlorinating bacteria. A consensus sequence is constructed by Ebersole, but this is done manually (see line col 9 lines 17-18 where it states "a consensus sequence was manually constructed"). Instead, software as described at col 9, lines 19-22 was

used to conduct similarity searches. The Applicants' invention does not need similarity searches. With regard to consensus sequences, as explained above, a consensus sequence of length N may not be the most common sequence in a set of organisms and in fact may not even occur in any of the sequences from which the consensus was calculated. Consensus sequences are not used in the applicant's method, which instead examines every subsequence of length N whether it is frequent or rare. Sequences that never occur or only occur once in the data set being used (as might be the case for a consensus sequence) can usefully be excluded (optional step C of claim 4). Ebersole's use of consensus sequences is emblematic of an entirely different method from the present invention.

> *Ebersole et al. further teach determining signature regions and sequences for identifying particular organisms, which are characteristic of those organisms. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have tabulated the extent to which the presence of each particular subsequence of length N is characteristic of each node in the bifurcating phylogenetic tree of genetic relationship by examining the occurrence frequency of each subsequence in the target nucleic acid to create a database of characteristic signature sequences in the method taught by Ebersole et al. This is because Ebersole et al. already considers how particular sequences are characteristic of individual and groups of organisms. One of skill in the art would have recognized that applying the known technique of tabulating the extent to which the sequences were characteristic of each node (i.e. group or individual organism) would have yield predictable results.*

This must be respectfully traversed. Past skilled researchers have not found the present invention obvious. The Kohne patent (US Patent 4,851,330) issued in 1989 described rRNA as a hybridization target that could be used for bacterial identification. In the ensuing years, numerous individuals including Ebersole (US patent 6,797,817); Barns *et al.* (US patent 5217862); Brentano et al., (US patent 7294489); Brentano et al., (US patent 6747141); Barbour et al., (US patent 6617441); Hester et al., (US patent 6855498); Barbour et al., (US patent 5932220); Aldrich et al., (US patent 5049489); Milliman (US patent 5830654); Wesley et al. (US patent 5202425) and others have described methodologies for detecting/identifying various specific microorganisms by taking advantage of

specific (i.e. preferably unique) sequences in 16S rRNA as targets for probes or PCR primers. Coleman (US patent 6738502) affirms that this is the prevailing view (col 5 lines 60-63 and col 2 lines 52-55). These individuals are certainly of at least ordinary skill in the art. That no one has previously recognized the important advantages of seeking to determine genetic affinity rather than genetic identity, and to seriously consider sequences of length N that may not be highly specific to a particular grouping strongly suggests that the AApplicants' invention is in fact not obvious to those of ordinary skill in the art.

Ebersole values "particular sequences (that) are characteristic of individual and groups of organisms" to such an extent that his emphasis is on those subsequences that are unique to his target group or specific organisms within the target group. For example, the emphasis on uniqueness is seen multiple times including Ebersole col 1, lines 13-15; col 4, lines 55-57; col 4 lines 55-58; col 5 lines 34-37; col 8 lines 30-34; and col 9 lines 43-46. This concentration on the great value of unique subsequences is precisely what causes Ebersole and others to overlook, and never teach the potential value of subsequences of length N that lack such uniqueness (page 9 lines 9-13) and might instead be associated with multiple groupings. Also, Ebersole's emphasis on uniqueness leads to the belief that each organism or group must be identified separately, and hence one must design a test for a particular targeted group. (Most of the patents cited in the previous paragraph in fact describe detection of specific target groupings using 16S rRNA). Thus, even the possibility that one can determine genetic affinity without knowing *a priori* what organism or virus may be in the test sample was not obvious to those of skill in the art. It is, however, featured in Applicants' invention as seen at page 4 lines 5-6; page 7 lines 11-14; page 8 lines 8-10; page 9 lines 11-17.

Likewise, it is not obvious to those of ordinary skill in the art that it is useful to examine the "occurrence frequency of each subsequence in the target nucleic acid of the organisms or viruses encompassed by or not encompassed by each node in the tree" as recited in claim 4 step D and claim 40 of the AApplicants' invention. The value of this is emphasized at Applicants' Specification e.g. at page 6 lines14-22; page 7 lines 1-3; and page 9 lines10-12. An examination of the results for branch node 5547 in the sample results shown in Table F on page 57 illustrate that even though no unique subsequence of length 9 or longer could be found for this node, it would still be possible to identify it, using any of multiple subsequences of length 9 or more that had high (0.8-0.99) but not perfect values of Q_s

Ebersole et al. teach claims 5 and 41 -42 at col. 2, lines 50-59 wherein rDNA are used for obtaining probes, which reads on the use of DNA for comprising signature probes.

Claims 5, 41 and 42 are dependent on claim 4, which is in itself distinct from Ebersole as argued above.

[Page 12] Ebersole et al. teach claim 6 at col. 6, lines 58-67 wherein hybridization is taught which is consistent in the art wherein a hybridization step is done in solution, which reads on claim 6.

Claim 6 is dependent on claim 4, which is in itself distinct from Ebersole as argued above.

Ebersole et al. teach claim 7 at col. 13, lines 25-30 wherein it is taught that probes which generate a detectable signal are used, which makes obvious a probe wherein the detection step utilizes radioactive labels, chemiluminescence, and/or fluorescence.

Claim 7 is dependent on claim 4, which is in itself distinct from Ebersole as argued above.

Ebersole et al. teach claim 9, of defining a grouping ora specific species, i.e. dechlorinating bacteria, see Col. 9, lines 35-45.

Claim 9 is dependent on claim 4, which is in itself distinct from Ebersole as argued above.

Ebersole et al. teach limitations of claim 10 as follows: at col. 9, lines 45-67 and col. 10 Ebersole et al. teach using a 16S rDNA profile of the isolated dechlorinators to compile profiles, i.e. database, of at least 12 nucleic acid sequenes (co1.10, lines 40-

> *49 describe at least 12 different variations of sequences usable for diagnostics of the dechlorinating bacteria) as in step A).*

Ebersole's profiles (col 9 lines 47-48) are defined as being complete 16S rRNA sequences (col 5 lines 30-31) and that is what is shown in Figure 1 and 2. Figure 1 show sequence alignments between complete 16S rRNA sequences of various dechlorinators. Figure 2 shows a joint alignment of *E. coli* 16S rRNA with the dechlorinator 16S rRNA sequences. In Figure 1, only six sequences are used and in Figure 2, only seven sequences are used whereas claim 10 part A specifies that at least 12 target nucleic acid sequences should be used. The 12 that the examiner points out actually refers to the numbers of variations seen, not the number of target sequences initially used. In addition, the applicants' invention does not employ sequence alignment (see example in specification-page 15, line 6) and uses subsequences not complete sequences when identifying characteristic subsequences.

> *Ebersole et al. further describes variations of subsequences and at Fig. 1-2 and table 2 tabulates these differences and distributions as in step B).*

Ebersole fails to examine all subsequences of length N as is done in Part B of claim 10 and does not even define what values of N are being considered. In addition, Ebersole does not calculate occurrence frequency but rather just tabulates individual changes.

> *Ebersole et al. further evaluates the extent to which subsequence variation is characteristic of each species of dechlorinating bacteria, I.e. node, which reads on step C).*

As pointed out in the discussion of claim 4, if the cluster of dechlorinating bacteria actually contains within it multiple additional nodes, e.g. the sub-types then what is the phylogenetic relationship between these various subtypes? If Ebersole is relying on a phylogenetic tree as in the instant invention, then why is such a tree not calculated or obtained from elsewhere? Part C of claim 10 clearly asserts that each node must be examined but how can this be done if those nodes are not

defined. Finally, Claim 10 is dependent on claim 4, which is in itself distinct from Ebersole as discussed above.

> *Ebersole et at. suggest, but do not explicitly teach wherein the tree comprises 11 or more nodes as in claim 39 and a limitation in claim 45. Ebersole et at. suggest this because they teach at col. 1-2 a method of identifying several species of dechlorinating bacteria, which uses phylogenetic relationships.*

At Ebersole's col 2 lines 17-19, it is pointed out that the 16S rRNA sequence information "was initially used for phylogenetic analyses but it has been more recently used for DNA probe-based methods for identification of organisms." If Ebersole believes that phylogenetic analysis is not used when developing probe-based methods then one can infer that knowledge of phylogenetic relationships is not needed in Ebersole's invention. Furthermore, Ebersole is focused here as pointing out by the examiner focused on determining genetic identity not affinity.

> *[Page 13] Ebersole et al. further teach at col. 2, lines 60-65 being able to identify new strains of dechlorinating bacteria.*

At col 2, lines 60-65 Ebersole suggests using primers. This implies that identification of new strains can be accomplished by amplification, sequencing and a Pearson and Lippman similarity search as is in fact is described in detail atEbersole col 9 lines 11-22. When sequences were subsequently available, they were compared to the *Dehaloccoides enthenogenes* strain 195 with similarities ranging from 98.5-99.6%. The sequences are designated *Dehaloccoides enthenogenes* –like 16S rRNA sequences (col 22, lines 57-6). The Applicants' method does not use sequencing technology to determine genetic affinity and does not rely on direct comparison of aligned sequences (specification page 15, line 6).

At col 2, Lines 60-65 Ebersole also suggests using probes to identify new *Dehaloccoides enthenogeness* strains. As revealed by the sequencing studies (col 22 lines 44-67; col 23 lines 1-41; and Table 2) some strains exist that have

sequence variations relative to *Dehaloccoides enthenogene* strain 195, such that any probe exactly targeting strain 195 may fail to detect some of the *Dehaloccoides enthenogenes* –like strains. In that event the novel strain would be completely undetected by the methods of Ebersole. In contrast, when determining genetic affinity in the manner of the instant invention, Applicants would learn that something was present with a partial identification such as being a member of the genus *Dehaloccoides.*

> *It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used a tree comprising 11 or more nodes for use in the method of identifying bacteria as taught by Ebersole et al. This is because Ebersole et al. teach a method of using a tree of nodes for help in identifying dechlorinating bacteria.*

As the examiner points out, Ebersole is providing methodology for identifying bacteria whereas the applicants' invention seeks to determine genetic affinity. Finally, since a tree of phylogenetic relationships is not relied on or utilized by Ebersole when identifying signature sequences, Ebersole should not be interpreted as suggesting a tree of more than 11 nodes as this relates to claims 39 and 45.

> *It would have been obvious to one of ordinary skill in the art that as new/ i.e. more dechlorinating bacteria are identified, see col. 2, lines 60-65, that any phylogenetic tree used in the identification process would also comprise more nodes. Therefore, the use of 11 or more nodes in a phylogenetic tree opposed to fewer than 11 nodes, is a result of an optimized parameter and not the product of innovation. The differences between the claimed invention and the prior art were encompassed in known variation or in a principal known in the prior art.*

The Applicants' invention seeks to establish genetic affinity and not genetic identity and therefore although the number of nodes available may increase due to the availability of more data, the number of nodes chosen may not change. In seeking to determine genetic affinity the number of nodes chosen will be governed by which groupings one wants to include in the analysis not the number of nodes that are available. Thus, if one wanted to screen for members of various genera in the phylum Chloroflexi, it would not matter that numerous new sequences were available for subgroups of *Dehalococcoides enthenogenes* as the only feature of

interest is whether or not anything with affinity with the genus *Dehalococcoide* is present. Furthermore, claims 39 and 45 are dependent on claim 4, which is in itself distinct from Ebersole as discussed above.

> *Ebersole et al. suggest, but do not explicitly teach where the same target nucleic acid sequence is obtained from at least 12 organisms or viruses as in claim 44 and a limitation of claim 45.*
> *Ebersole et al. suggest this because they teach at col. 1-2 a method of identifying several species of dechlorinating bacteria, which uses phylogenetic relationships and several nucleic acid sequences. Ebersole et al. further teach at col. 2, lines 60-65 being able to identify new strains of dechlorinating bacteria.*
> *It would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used the same target nucleic acid sequence obtained from at [Page 14] least 12 organisms or viruses for use in the method of identifying bacteria as taught by Ebersole et al. This is because Ebersole et al. teach a method of using a tree of nodes for help in identifying dechlorinating bacteria.*

The data on additional dechlorinating 16S rRNA sequences described by Ebersole at col 2, lines 60-65 and in detail at col 22 lines 44-67 and col 23 lines 1-41 would be sufficient to construct a tree of additional nodes within the dechlorinating group. Despite this, Ebersole makes no mention of parsimony, or any other tree constructing program in the context of analyzing these additional sequences. The amount of sequence identity of various isolates with *Dehalococcoides enthenogenes* strain 195 is calculated following alignment of sequences and is found to be in the range of 98.5 to 99.6% (col 21 lines 45-47). In addition, similarities of the various individual isolates (col 23 lines 5-13) with *Dehalococcoides enthenogenes* strain 195 are reported. However, the % similarities among the individual new isolates are starkly missing. A matrix of the similarity between all pairs of isolates is used in tree making methods of the distance type. The fact Ebersole is not calculating this information that is central to tree construction illustrates that he is not in fact utilizing a tree. Instead, Ebersole relies on sequence alignment. Hence claim 4 and 45 and their dependent claims are distinct from Ebersole. Furthermore, claim 44 is dependent on claim 4, which is in itself distinct from Ebersole as argued in this section and above.

It would have been obvious to one of ordinary skill in the art that as new! i.e. more dechlorinating bacteria are identified, see col. 2, lines 60-65, that more sequences would be used in the identification process. Therefore, the use of sequences from 12 or more organisms or viruses fewer organisms or viruses, is a result of an optimized parameter and not the product of innovation. The differences between the claimed invention and the prior art were encompassed in known variation or in a principal known in the prior art.

Ebersole et al at col. 9 and col. 10, teach using consensus sequences for identifying signature regions, i.e. signature sequences, wherein the sequences comprise at least 12 (see the 16s rONA base substitutions of the consensus sequences. which when taken independently or together are usable for a diagnostic for dechlorinating bacteria), and the consensus sequences are at least 30% identical over at least one subsequence of at least 50 nucleotides (see SEQ 10 NO: 34) as in claim 46.

As discussed with reference to claim 4 the use of consensus sequences and sequence regions teaches away from the applicants' invention. In addition, claim 46 is dependent on claim 4, which is in itself distinct from Ebersole as argued above. In addition, as discussed in previous communications the "signature sequences" of Ebersole are defined differently than in the applicants' invention.

Ebersole et al. teach at col. 9, lines 46-65 teach using consensus sequences of length 7 or longer that occur in all the dechlorinating isolates when creating a profile, i.e. database of signature sequences as in claim 47.
[Page 15]

As explained in the discussion of claim 4 above, a consensus sequence of length N may not be the most common sequence in a set of organisms and in fact may not even occur in any of the sequences from which the consensus was calculated. Consensus sequences are not used in the applicant's method, which instead examines every subsequence of length N whether it is frequent or rare. If a consensus sequence were used it might, in accordance with claim 47, be excluded from the analysis. In addition, Claim 47 is dependent on claim 4, which is in itself distinct from Ebersole as argued above. Ebersole defines the term "16S rDNA profile" at col 5 line 29-30 as "the specific DNA sequence of the rDNA gene in any particular organism". Such profiles are not created, but rather determined by sequencing the particular 16S rDNA. Hence, the profile is a particular sequence

and not a database of signature sequences as described in claim 47. In addition, claim 47 is dependent on claim 4, which is in itself distinct from Ebersole as argued throughout.

> *Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ebersole et al. (US PIN 6,797,817) as applied to claim 4 above, and further in view of Coleman et al. (US PIN 6,738,502).*
> *Ebersole et al. teach claim 4 as described above in the instant office action. Ebersole et al. suggest do not explicitly teach generating the bifurcating phylogenetic tree of relationship by parsimony method.*
> *Ebersole et al. suggest this because they teach using and creating a phylogenetic tree of organisms and in particular bacteria.*
> *Coleman et al. teach at col. 2, lines 45-49 and col. 5, lines 50-57 a method directed to using 168 rRNA sequence information to deduce a phylogenetic relationship based on a parsimony method.*
> *It would have been obvious to one ordinary skill in the art at the time of the instant invention to have used a parsimony method for creating a phylogenetic relationship as taught by Colman et al. for use in the method of using sequences and phylogenetic relationships for identifying bacteria as taught by Ebersole et al. Creating a phylogenetic tree by a parsimony method is a well known method as taught by Coleman et al. One of ordinary skill in the art would have substituted one known element, i.e. deducing a phylogenetic tree based on parsimony for another method of deducing a phylogenetic tree, and the results of the substitution would have been predictable. The differences between the claimed invention and the prior art were encompassed in known variations or in a principal known in the prior art.*

In fact the applicants' method can simply use a tree from another source as was done in the example in the specification (page 16, lines 7-8). Therefore parsimony and other tree making methods are not essential. It is only necessary to have a hierarchical classification that includes the organism groups of interest. Claim 8 is dependent on claim 4, which is in itself distinct from Ebersole as argued above,

There is no suggestion that Coleman's optical method be combined with Ebersole's targeted consensus sequence method. Even if it somehow were, neither reference nor their combination would make obvious the present invention.

> *[Page 16] Conclusion*
> *No claim is allowable.*

The present invention obtains vastly more information than Ebersole obtains in his presence/absence testing for his specific target organisms. Applicants seek to determine the genetic affinity of an unknown organism in the context of a hierarchical system while Ebersole seeks to determine if an unknown organism belongs to a single grouping. Even if Ebersole's one group might be considered to itself contain subgroups, e.g. additional nodes, Ebersole does not construct or utilize a tree to examine such subgroups. Indeed he teaches away from the use of phylogenetic information by failing to compute all the distances that would be needed to construct a distance tree. Instead he relies on consensus sequences that are never needed and not used in the Applicant's invention. Applicants invention looks at many nodes in a hierarchical system of interest, e.g. tree; while Ebersole looks at in effect one node and therefore doesn't utilize phylogenetic relationship data when identifying his signature regions. Applicants examine in-group and out-of-group occurrence frequencies of substantially all n-mers found in a set of target nucleic acids. In contrast in order to identify signature sequences, Ebersole aligns complete sequences. His complete sequences are never fragmented into n-mers during the process used to identify suitable signatures. Instead. Ebersole visually identifies "signature regions" in the still complete sequences from which small numbers of N-mer probes are designed. Ebersole's final probes are N-mers, but his N-mers are not used in the design processs as is done in the Applicants' invention.

Not only is Applicants' claimed method unobvious, it has unexpected advantages not even hinted at by the Prior Art. Allowance of the claims is now urged to be required under the mandate of 35 USC 101.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason Sims, whose telephone number is (571)-272-7540.
If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Marjorie Moran can be reached via telephone (571)-272-0720.
Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16,1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d». The Central PTO Fax Center number is (571)-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).
Jason Sims / Marjorie Moran SPE Art Unit 1631

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The Amendments herein are merely clarifying wording and no estoppel or new matter is involved; they are not required to distinguish from prior art.

Any necessary (small entity) charges can be charged to USPTO Deposit Account 200336 of Technology Licensing Co. LLC. Correspondence may be addressed to Customer No. 26830.

The Examiner is especially invited to telephone Applicants' Attorney if that would expedite prosecution and disposal of this Application.

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by the inventor of carrying out his invention.
Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
Claim 5 comprises a step wherein signature probes comprise a moiety selected from the group consisting of RNA, DNA, an analog of RNA or DNA including peptide nucleic acids, 2-0-methyl DNA and any other molecule that can interact with the test sample, wherein the wording "any other molecule that can interact with the test sample nucleic acid in a sequence-specific way" lacks support in the instant specification. Support for "any other molecule," such as ribosomal proteins, antibodies, or any regulatory element, etc. has not been found in the specification. As such, claim 5 lacks adequate written description of sufficient species to show possession of the genus of "any other molecule."

The examiner is correct in pointing out that the prior language of Claim 5 might in principle allow for interactions with other molecules that interact with RNA or DNA in a sequence specific way such as a polymerase recognizing a promoter. The intent of the claim is to emphasize that the signature probe may be comprised of any of a wide variety of nucleic acid types. The revised claim accomplishes this by specifying that the "other molecule" is a nucleic acid and relies on complementarity, i.e. common Watson-Crick base-base interactions.

In support of this claim, hybridization is first taught on pages 3 of the specification where a set of signature oligonucleotides is utilized in a hybridization experiment, e.g. a DNA microarray, the results of which are then used to quickly identify the phylogenetic neighborhood of a problematic bacterium, or other microorganism. Hybridization is in fact taught in many other places in the specification as well. Peptide Nucleic Acids are taught in Applicants' Example 3 which shows an array of all possible 8-mer peptide nucleic acids. Table G on page 60 under detection means teach the use of peptide nucleic acids branched DNA hybridization. 2' O-methyl is supported on page 33 line 6 of the specification where the signature probes are comprised of a nucleic acid analog comprising